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08/591,651	02/12/1996	JOHN B. CLASSEN	CLASSEN=1A	9417

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EXAMINER	
GAMBEL, PHILLIP	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/591,651	CLASSEN, JOHN B.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-61,84,108,116,277-279,281,292,294,298-301 and 304-324* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-61, 84, 108, 116, 277-279, 281, 292, 294, 298-301 and 304-324* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/02/2009, 09/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center Art Unit 1644.

2. Applicant's request for a telephonic interview before the examiner works on this amendment in the Remarks, filed 09/21/2009, is acknowledged.

However, given the transfer of this application to another examiner and the New Grounds of Rejection set forth herein, it is deemed that an interview after receiving this Office Action would be more productive.

Also, note that given the number of issues presented previously and herein, applicant should address the New Grounds of Rejection set forth herein.

Not all issues presented in applicant's Remarks filed 09/21/2009 will be addressed herein unless they are still deemed pertinent to the current Office Action.

The examiner apologizes for any inconvenience to applicant in this matter.

3. Applicant's amendment, filed 09/21/2009, has been entered.

Claims 1-58, 62-83, 85-107, 109-115, 117-276, 280, 282-291, 293, 295-297 and 302-303 have been canceled.

Claims 59, 84, 108, 116, 177-179, 281, 292, 294 and 298-301 have been amended

Claims 304-324 have been added.

Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are pending.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention (e.g., methods are not claimed).

5. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent

application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should update the status of USSN 08/104,529 on page 1 of the specification.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

7. Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are indefinite under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as they do not recite clear and definitive method steps and appear to be incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The claimed methods comprise methods of "comparing the risk, incidence, prevalence, frequency or severity of a chronic immune-mediated disorder, or the level of a marker of a disorder", risk...", "comparing the risk...", "according to an immunization schedule...", "associations are statistically significant", wherein the risk of a chronic immune mediated disorder is determined, "adequate protection", and "substantially reduce the incidence or severity of said chronic immune-mediated disorder" for example.

The metes and bounds of the immunization schedule(s), the nature of the immunogens / markers and their relationship to a chronic immune-mediated disorder as well as the parameters that are being employed in comparing the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group are ill-defined and ambiguous.

For example, the specification describes an immunization schedule as a program for the administration of one or more specified doses of one or more specified immunogens, by one or more specified routes of administration, at one or more specified ages of the immunization subject. A supplemental immunization schedule is one intended to supplement a standard immunization schedule which is commonly followed in the region in which the subject resides.

However, there are no parameters to provide a standard for ascertaining the requisite degree or direction and, in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention or the parameters by which to compare the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder (e.g., level, specificity of response, specificity of disorder) in the treatment group with that in a control group.

The specification is replete with descriptions of immunogens, agents, immunization schedules and methods of determination, but lacks a clear specificity as to which markers and corresponding values permits one to evaluate the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder.

Applicant is invited to review the claims carefully and consider amending the claims to recite a sufficient number of positive steps, ingredients, testable functions and parameters to accomplish the claimed methods, provided there is written description in the specification as filed.

The specification is replete with descriptions of immunogens, agents, immunization schedules and methods of determination, but lacks a clear specificity as to which markers and corresponding values permits one to evaluate the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder.

Therefore, the nature and parameters with respect to the claimed "comparing steps" are not clearly defined by the claims and the specification does not provide a standard for ascertaining the requisite degree or direction, in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention or the parameters by which to determine said metes and bounds.

Further, applicant's remarks, filed 09/21/2009, appear to rely upon the newly added limitations, in part, to impose limitation on the specific immunogens recited in the kits.

In turn, the claims are indefinite in terms of weight afforded to the "comparing steps" being claimed.

For example, are the comparing steps to be viewed as product-by-process limitations or as intended use limitations or both?

It is unclear how much weight should be given the structural limitations of the claim.

For example, if the kits comprising immunogens or the methods of making kits are provide with immunogens, merely comprise known compositions,

then the "comparing steps appears to carry little weight absent evidence of structural differences.

For example, a dose of an immunogen achieving any measurable amount of inducing an immune response in a human to an infectious disease should read on the claims.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. This is a rejection under 35 U.S.C. § 112, first paragraph, "written description" / new matter.

Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:
The recitation of the process of "comparing the incidence, prevalence, frequency or severity of a chronic immune-mediated disorder ..." and/or "comparing the risk..." as recited in the independent claims,
the recitation of "at least two different", "each conjugated to at least one", at least two different acellular", at least two purified viral capsid" of each of the immunogens recited in independent claim 59,
to which a human is susceptible" as recited in claim 59 and
where said immunogenic agent comprise a first carbohydrate immunogen conjugated to a first carrier protein and a second carbohydrate immunogen conjugate to a second and a different carrier protein as recited in claim 279.

The specification as filed does <u>not</u> appear to provide sufficient written description for these "limitations"

The description should clearly convey to the skilled artisan that the inventor had possession of the claimed subject matter at the time the invention was made.

Here, it appears that applicant has picked and chosen various elements of the specification to create new species or sub-generic claims.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

In the context of the conjugates, applicant's remarks, filed 09/21/2009, rely upon what the person skilled in the art would infer after reading the specification.

In addition, applicant's remarks rely upon incorporation all patents and articles cited anywhere in the specification.

For example, applicant's remarks, filed 09/21/2009, rely upon other patents of this patent family to add the comparison steps to the kit claims.

Applicant is reminded that to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re Seversky, 177 USPQ 144, 146 (CCPA 1973).

Also see Cook Biotech Inc. v. Acell, Inc., 79 USPQ2d 1865, 1872 (Fed. Cir. 2006) and Zenon Environmental Inc. v. United States Filter Corp., 85 USPQ2d 1118, 1124 (Fed. Cir. 2007)

In contrast to applicant's inferences and broad incorporation by reference are not sufficient direction and guidance to the particularities currently being claimed.

With respect to "susceptible humans", it is noted that this phrase is not readily apparent in the specification as filed.

Further, if applicant is trying define a subpopulation of humans, then this would be considered new matter, as there is insufficient written description of such subpopulations of "susceptible humans".

The claims represent a departure from the specification and claims as originally filed. Applicant's reliance on generic disclosure and possibly a single or limited species do/does not provide sufficient direction and guidance to claim "at least two"... as recited in the newly added sections (1)-(4) in independent claim 59 as well as the particular conjugates recited in claim 279.

The specification does not provide sufficient blazemarks nor direction for broadly claiming nucleic acid molecules that encode B7, as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06.

10. This is a rejection under 35 U.S.C. § 112, first paragraph, "written description" (and not new matter).

Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing:

a) comparing the incidence, prevalence, frequency or severity of a chronic immune-mediated disorder, or the level of a marker of such a disorder, in a treatment group of humans immunized according to an immunization schedule with one or more doses of said immunogen, with that in a control group of humans
and/or

b) comparing the risk of a chronic immune-mediated disorder in a first group of humans immunized according to an immunization schedule with one or more doses of said immunogen, with that in a second group of humans, said first group of humans having been immunized with one or more doses of said immunogen according to a first screened immunization schedule, and the second group of humans having been immunized with one or more doses of said immunogen according to a second screened immunization schedule, each group of humans having been immunized according to a different immunization schedule,

said immunization of (a) or (b) inducing an immune response, comprising production of antibodies or activation of T-cells, in at least one such group

Further, it is noted that the independent claims employ the comparing steps of (a) and/or (b) in the context of being "safe according to these methods (e.g., see claim 59), prophylactically or therapeutically in the immunization" (e.g., see claims 318) and "protective against one infectious disease" (e.g., see claims 278 and 318).

The recited methods are drawn to methods of "comparing the risk, incidence, prevalence, or severity of a chronic immune-mediated disorder" and "levels of a marker of such a disorder"

However, the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the immunogens, immunization schedule and markers in terms of the comparisons based upon the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group", are not set forth in the specification as filed, commensurate in scope with the claimed invention.

For example, the specification describes an immunization schedule as a program for the administration of one or more specified doses of one or more specified immunogens, by one or more specified routes of administration, at one or more specified ages of the immunization subject. A supplemental immunization schedule is one intended to supplement a standard immunization schedule which is commonly followed in the region in which the subject resides.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See MPEP 2163. Also, see The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, □ 1 "Written Description" Requirement.

Here, it appears that the claims recite a description of a problem(s) to be solved while claiming all solutions to it.

Several variables are used in evaluating the predictability of the process elements of the claimed kits, which essentially rely upon detection or diagnostic assays as they read on the claimed methods of comparing" encompassing "immunogens, immunization schedules, markers and comparisons based upon the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in a control group.

These variables include diagnostic specificity and sensitivity and positive and negative predictive values.

The diagnostic sensitivity of an assay reflects the fraction of those subjects with a specific disease that the assay correctly identifies as positive.

The diagnostic specificity of an assay reflects the fraction of those subjects without the disease that the assay correctly identifies as negative.

The positive predictive value refers to the probability that an individual with a positive test result has the disease.

The negative predictive value refers to the probability that an individual with a negative test result does not have the disease.

There is an inverse relationship between the sensitivity and specificity, which is related to the assigned cutoff value that is used for a particular test to segregate diseased populations from those with no disease.

The relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the "immunogens, immunization schedule, markers and comparisons based upon the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group" are not set forth in the specification as filed, commensurate in scope with the claimed invention

In an epidemiologic study to evaluate the possibility that timing of vaccination is related to risk of clinical diabetes in children, DeStefano et al. (Pediatrics 108: 1-5, 2001) present results that do not support this hypothesis but rather show that ht risk of type 1 diabetes was not different between infants vaccinated at birth and those who receive their first vaccination later in life. These results of the study and the preponderance of epidemiologic evidence do not support an associate between any of the recommended childhood vaccines and an increased risk of type 1 diabetes. Suggestion that diabetes risk in humans may be altered by changes in the timing of the

vaccination are unfounded (see entire document, including Conclusions on page 1, column 2, Discussion and Conclusion on page 4-5).

Further in addressing the possibility that vaccination may increase the risk of type 1 diabetes has been evaluated in a few epidemiologic studies, DeStefano et al. notes the following limitations on the observations encompassed by the instant invention (see page 4, column 1).

Classen has provided the only evidence of a possible increased risk, but the nature of the evidence is strictly ecological, involving comparisons between countries or between different time periods in the same country. Such comparisons, however, may be influenced by many factors unrelated to vaccination, such as genetic predisposition and other environmental exposures. Moreover, similar ecological analyses conducted by other investigators have not found significant correlations between diabetes and several vaccines, including BCG, pertussis, and mumps.

None of the epidemiologic studies that included control or comparison groups have found an increased risk of type 1 diabetes associated with vaccination. One of the largest and most comprehensive was a case-control study conducted in Sweden in the mid-1980s. Overall, the 339 cases and 528 controls had similar vaccination histories for BCG, smallpox, pertussis, tetanus, rubella, and mumps vaccines. The only significant difference was a decreased risk of type 1 diabetes associated with measles vaccination. In a retrospective cohort study conducted in Canada, no association was found between BCG vaccine and risk of diabetes, although there was a suggestion that vaccination may have delayed the onset of diabetes. A 10-year follow-up study of over 100 000 Finnish children who participated in a clinical trial of Hib vaccine also did not find an increased risk of diabetes

In an effort to determine if vaccinations and infections are associated with the subsequent risk of Type I insulin-dependent diabetes mellitus in childhood, The EURODIAB Substudy 2 Study Group makes the following conclusion or interpretation (Diabetologia 43: 47-53, 2000) (see entire document, including Abstract). It seems likely that the explanation for these contrasting findings of an increased risk associated with perinatal infections coupled with a protective effect of pre-school day care lies in the age-dependent modifying influence of infection on the developing immune system (e.g., see Conclusion/Interpretation on page 47 and Discussion on pages 51-52).

Further with respect to distinctions between animal models and humans, The EURODIAB Substudy 2 Study Group noted that the hypothesis that early exposure to infection can reduce the risk of diabetes has advocates but that the epidemiological evidence is, however, still weak and the hypothesis must remain speculative even though there is clear evidence to support it from animal models (e.g., see page 52, column 1, paragraph 2).

Wraith et al. reviews the evidence concerning the association between vaccination and autoimmune disease (Lancet 362: 1659-1666, 2003) (see entire document) and notes a number of principles and limitations on diagnosing or reducing vaccine-related autoimmune disease, which has to be assessed on a case-by-case basis (e.g., see How Can a doctor assess a potential link on page 1664) and that a clear distinction should be made between autoimmunity and autoimmune disease (e.g., see Concluding Remarks on page 1665).

Also, see Panel 1: Frequently Asked Questions About Autoimmunity and Autoimmune Diseases on page 1660 as follows.

Autoimmunity is a situation characterized by the development of one or several abnormal immune responses, directed against antigenic components of the host. Autoimmunity can lead to autoantibodies (antibodies against host antigens) or to autoreactive T cells (lymphocytes). Autoimmunity is not always result in autoimmune disease.

Autoimmune disease is a disease that results from autoimmunity, when pathogenic autoantibodies or autoreactive T cells (cell-mediated autoimmune disease) can reach corresponding targets (epitopes) with the appropriate configuration of presentation in host tissues.

In discussing Frequently Asked Questions about Vaccination and Autoimmunity (see Panel 3: Frequently Asked Questions About Vaccination and Autoimmunity on page 1661), Wraith notes the following:

In response as to which autoimmune disease, if any, have been proven due to vaccines;
it was noted that an Acute disseminated encephalomyelitis in 0-1% of a form of rabies vaccine, cases of Guillain-Barre neuritis arising after vaccines with swine influenza virus (albeit a rare event), and autoimmune thrombocytopenia has been described

In response to as to how can one demonstrate or exclude that a vaccine caused an autoimmune disease;
It was noted that only epidemiological studies or clinical trials with an extremely large sample size can allow for a consistent assessment of the relative risk of vaccine-related increased incidence, wherein such studies with large sample size are complex, difficult to do and costly, which limit their availability as to how can one demonstrate or exclude that a vaccine caused an autoimmune disease.

In response as to whether minimum criteria be established for diagnosing vaccine-related autoimmune disease,
it was noted that there exist no general criteria and this question has to be analyzed on a case-by-case basis.

In addressing the proposed link between childhood vaccinations and the development of type 1 diabetes, Hviid et al. concludes based on their study on childhood vaccination in Denmark (N. Eng. J. Med. 350: 1398-1404, 2004) (see entire document, including Abstract and Discussion).

Also, Hviid et al. describes the basis for the proposed link and the lack of evidence supporting this proposed link, including the examples relied upon in the instant specification, as follows on page 1399, column 1, paragraph 2.

A link between childhood vaccinations and the development of type 1 diabetes has been proposed for several reasons. First, there is a temporal association between the widespread introduction of general childhood immunizations and the increase in the incidence of type 1 diabetes in developed countries. Second, it has been observed that specific vaccines prevent type 1 diabetes in murine models and others induce it. And third, some findings suggest an association between infections and type 1 diabetes. In particular, it has been hypothesized that any vaccination after two months of age increases person's risk of type 1 diabetes and that early vaccination (in the first month of life) protects against type 1 diabetes. Vaccination against Haemophilus influenzae type b has been singled out, with claims of clustering of cases of type 1 diabetes three to four years after vaccination. This hypothesis has recently been expanded to include bacille Calmette–Guérin vaccine; measles, mumps, and rubella (MMR) vaccine; and pertussis vaccine. However, the majority of the evidence does not provide support for these specific hypotheses or for any other association between type 1 diabetes and childhood vaccination, yet there have been few analytic studies.

In discussing biomarkers for diagnosing and monitoring autoimmune diseases activity (Prince, Biomarkers 10 Supplement 1: S44-S49, 2005) (see entire document),

Prince concludes that many proteins are increased at tissue sites affected by autoimmune diseases, but only a small number of them show promise as useful markers and much more work is need to characterize changes in response to treatment even that progress has been made in relating the levels of these proteins to disease (see Conclusion on page 548).

Prince also notes that autoantibodies are typically not good biomarkers, mainly because they tend to remain detectable, even after successful treatment (e.g., see page S45, lines 1-2).

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pathogenic processes or pharmacological responses to a therapeutic intervention.

Such markers are useful for diagnosis, prognosis, therapy and drug development and must be based on and follow the understanding of the pathological basis of the disease under study. Measures of the disease process are distinguished between those that have utility in clinical care, where they are called biomarkers and those useful in therapeutic trials, where thy are referred to as surrogate end points. The term surrogate marker is confusing. The requirement for a surrogate end point are multiple and difficult to realize. From the particular view of a diagnostic procedure, a biomarker would need to identify individuals at risk of a given disease and monitor progression towards clinically overt disease. This step would be exceptionally useful in a disease of uncertain evolution / etiology. However, markers must monitor disease progression the clinical manifestation and reflect the extent of intervention afterwards. Other ideal characteristics are that such markers should be applicable in terms of screenings, implying a simple and minimally invasive sample acquisition and processing procedures.

See entire document of Biomarkers Definitions Working Groups., Clin. Pharmacol. Ther. 69: 89-95, 2001.

Given that biomarkers / surrogate markers often do not provide sufficient reproducibility and are difficult to standardize,

that difficulties in relying upon biomarkers / surrogate markers relate to the heterogeneity of diseases and multiple targets such as encompassed by the claimed chronic immune-mediated disorders,

that additional obstacles are raised by high variability in the nature of chronic immune-mediated disorders (e.g., autoimmune diseases) and

that the pathophysiological processes of diseases including chronic immune-mediated disorders, are interconnected and any single marker would be insensitive to completely capture the effect of therapeutic applications;

there is insufficient written description to the claimed methods of determining an immunization that the affects the incidence or severity of a chronic immune-mediated in treatment groups relative to control groups, based upon comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.

Note, too, that the evidence provided herein indicates that reliance upon the murine models of diabetes described in the specification does not translate to the association of vaccination and human chronic immune-mediated disorders such as autoimmunity, including diabetes, in humans.

There is an insufficient understanding of the pathogenesis of the diseases and markers that would lead the skilled artisan to make a judgment on the clinical factors, correlation of results with the clinical characteristics of the diseases, such as relapse or progression and response to therapy in a field which is controversial and still debated such as the case here concerning the association of chronic immune-mediated diseases such as autoimmune diseases and vaccination, particularly childhood vaccination.

The evidence would indicate that there is an inability to discriminate between determining whether an immunization protocol can affect the incidence or severity of a chronic immune-mediated in treatment groups relative to control group or whether an immunization protocol can be design to affect the incidence or severity of a chronic immune-mediated disorder, broadly encompassed by the claimed methods.

For example, the level or specificity (e.g., antigen specificity) of antibody production or T cell activation is lacking in terms of the claimed methods.

In the absence of objective evidence to the contrary and keeping with the nature of evaluating a number of potential immunological markers for determining an immunization that the affects the incidence or severity of a chronic immune-mediated in treatment groups relative to control groups encompassed by the claimed methods,
the skilled artisan would predict that either there is little or no association between immunization schedules, including childhood vaccination schedules, and chronic immune-mediated disorders or that there is an overlap between diseased and non-diseased groups.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The written description requirement also ensures that when a patent claims a genus by its function or results, the specification recites sufficient materials to accomplish that function- a problem that is particularly acute in the biological arts.

See Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1105-1106 (Jan. 5, 2001) and Ariad Pharmaceuticals Inc. v. Eli Lilly & Co., 94 USPQ2d 1161, 1172 (Fed. Cir. 2010).

Here, applicant has not provided sufficient possession of relevant identifying characteristics of the elements, parameters and/or steps of the claimed immunization schedule(s) and comparison(s) that would convey to the skilled artisan that the claims or the specification provide sufficient written requirements necessary to meet the sensitivity, specificity and controls for the claimed "methods of determining".

Knowing the starting point is not enough; that is little more than a research plan.
Consistent with the limitations of the murine models that suggest immunization at birth is associated with a decreased risk of diabetes (type I insulin-dependent diabetes mellitus; IDDM) and in associating vaccination with immune-mediated disorders in humans as well as being consistent with insufficiency of the immunization schedules addressing vaccines to immune-mediated disorders such as diabetes in humans at the time the invention was made, inventor's co-authored publication (Classen et al., Medical Hypotheses 57: 532-538, 2001) (see entire document, particularly the Conclusion on page 536) concludes with the following.

There are many mechanisms by which vaccines may affect the onset of IDDM or other immune-induced disorders. The predominant pathways may depend on individual genotype. We believe that lack of full comprehension of the mechanism of action does not detract from toxicology data linking vaccines to IDDM, nor does a complete knowledge of the mechanism of action need to be known before studying the potential benefits of new immunization schedules.

Here, Classen et al. recognize that immune-induced disorders may depend on individual genotypes and that immunization schedules addressing the association between immunization and immune-mediated disorders was still at the potential stage subsequent to the time the invention was made.

While the specification discloses a starting point for screening or testing for immunogens, immunization schedules and comparisons including markers to can determine an immunization schedules that affects the incidence or severity of a chronic immune-mediated disorder, the instant disclosure does not set forth sufficient procedures, elements and parameters that will necessarily lead to determine whether an immunization schedule could affect the incidence or severity of a chronic immune-mediated disorder and it does not identify correlations between vaccines and chronic immune-mediated disorders, including the appropriate immunogens, comparisons and markers to provide a sufficient number of species to support the claimed generic methods.

The application does no more than describe the desired function or endpoints of the claimed "methods of determining" broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon finding "an immunization schedule could affect the incidence or severity of a chronic immune-mediated disorder and it does not identify correlations between vaccines and chronic immune-mediated disorders", including the reliance upon the appropriate immunogens, comparisons and markers.

Without the appropriate immunogens, comparisons, markers and parameters, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the elements, parameters and comparisons that are essential to practice the method. Without possession of the claimed comparisons and/or correlations between vaccination / immunization and chronic immune-mediated disorders, the claimed endpoints are illusory and there is no meaningful possession of the method.

The description of claimed methods of determining an immunization that the affects the incidence or severity of a chronic immune-mediated in treatment groups relative to control groups, based upon comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group represents a wish or a plan for future research, but is insufficient for the written description of the claimed invention as of the filing date sought

The hallmark of written description is disclosure or possession as shown in the disclosure. The specification must describe an invention understandable to the skilled artisan and show that the inventor actually invented the invention claimed.
See Ariad Pharmaceuticals Inc. v. Eli Lilly & Co. 94 USPQ2d 1161, 1172 (Fed. Cir. 2010).

Here, the specification does not contain a sufficient written description of the claimed invention in that the disclosure does not does not describe the invention with particularity and reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision. (see page 1115.)

11. Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

A) "Methods of comparing ... ": Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324.

In vitro and animal model studies have not correlated well with "methods of comparing the incidence..." and/or "methods of comparing the risk..." as currently recited and encompassed by the claimed invention. Since "methods of comparing whether an immunization schedule affects the risk, incidence, prevalence, frequency or severity of a chronic immune-mediated disorder in a treatment group of mammals" can be species-/disorder-dependent, it is not clear that reliance on the in vitro and in vivo observations as well as the clinical experience with certain immunization schedules and chronic immune-mediated disorders accurately reflects the relative ability or efficacy of the claimed "methods of comparing..." broadly encompassed in the claimed kits and methods of making the kits.

For example, the claimed "methods of comparing the incidence..." and/or "methods of comparing the risk..." rely upon determining whether an immunization schedule affects the risk, incidence, frequency or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group upon "one or more doses or one or more immunogens" as well as comparing "markers".

The specification does not provide sufficient guidance and direction to identify and to enable (make and use) any "methods of comparing the incidence..." and/or "methods of comparing the risk..." based upon any immunogens (including those specifically recited)/ immunization schedule as well by any comparisons based upon the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group", in the specification as filed, commensurate in scope with the claimed invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Here, it appears that the claims recite a description of a problem(s) to be solved while claiming all solutions to it.

Several variables are used in evaluating the predictability of "methods of comparing the incidence..." and/or "methods of comparing the risk..."as they read on detection or diagnostic assays encompassing "immunogens, immunization schedules, markers and comparisons based upon the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group".

These variables include diagnostic specificity and sensitivity and positive and negative predictive values.

The diagnostic sensitivity of an assay reflects the fraction of those subjects with a specific disease that the assay correctly identifies as positive.

The diagnostic specificity of an assay reflects the fraction of those subjects without the disease that the assay correctly identifies as negative.

The positive predictive value refers to the probability that an individual with a positive test result has the disease.

The negative predictive value refers to the probability that an individual with a negative test result does not have the disease.

There is an inverse relationship between the sensitivity and specificity, which is related to the assigned cutoff value that is used for a particular test to segregate diseased populations from those with no disease.

There is insufficient guidance and directions as to how to make and use any "immunogen (including those specifically recited), immunization schedule, marker and comparison based upon the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of any marker of such a disorder, in the treatment group, with that in the control group" to affect the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals relative to a control group of mammals, commensurate in scope with the claimed invention

In an epidemiologic study to evaluate the possibility that timing of vaccination is related to risk of clinical diabetes in children, DeStefano et al. (Pediatrics 108: 1-5, 2001) present results that do not support this hypothesis but rather show that ht risk of type 1 diabetes was not different between infants vaccinated at birth and those who receive their first vaccination later in life. These results of the study and the preponderance of epidemiologic evidence do not support an associate between any of the recommended childhood vaccines and an increased risk of type 1 diabetes. Suggestion that diabetes risk in humans may be altered by changes in the timing of the vaccination are unfounded (see entire document, including Conclusions on page 1, column 2, Discussion and Conclusion on page 4-5).

Further in addressing the possibility that vaccination may increase the risk of type 1 diabetes has been evaluated in a few epidemiologic studies, DeStefano et al. notes the following limitations on the observations encompassed by the instant invention (see page 4, column 1).

Classen has provided the only evidence of a possible increased risk, but the nature of the evidence is strictly ecological, involving comparisons between countries or between different time periods in the same country. Such comparisons, however, may be influenced by many factors unrelated to vaccination, such as genetic predisposition and other environmental exposures. Moreover, similar ecological analyses conducted by other investigators have not found significant correlations between diabetes and several vaccines, including BCG, pertussis, and mumps.

None of the epidemiologic studies that included control or comparison groups have found an increased risk of type 1 diabetes associated with vaccination. One of the largest and most comprehensive was a case-control study conducted in Sweden in the mid-1980s. Overall, the 339 cases and 528 controls had similar vaccination histories for BCG, smallpox, pertussis, tetanus, rubella, and mumps vaccines. The only significant difference was a decreased risk of type 1 diabetes associated with measles vaccination. In a retrospective cohort study conducted in Canada, no association was found between BCG vaccine and risk of diabetes, although there was a suggestion that vaccination may have delayed the onset of diabetes. A 10-year follow-up study of over 100 000 Finnish children who participated in a clinical trial of Hib vaccine also did not find an increased risk of diabetes

In an effort to determine if vaccinations and infections are associated with the subsequent risk of Type I insulin-dependent diabetes mellitus in childhood, The EURODIAB Substudy 2 Study Group makes the following conclusion or interpretation (Diabetologia 43: 47-53, 2000) (see entire document, including Abstract). It seems likely that the explanation for these contrasting findings of an increased risk associated with perinatal infections coupled with a protective effect of pre-school day care lies in the age-dependent modifying influence of infection on the developing immune system (e.g., see Conclusion/Interpretation on page 47 and Discussion on pages 51-52).

Further with respect to distinctions between animal models and humans, The EURODIAB Substudy 2 Study Group noted that the hypothesis that early exposure to infection can reduce the risk of diabetes has advocates but that the epidemiological evidence is, however, still weak and the hypothesis must remain speculative even though there is clear evidence to support it from animal models (e.g., see page 52, column 1, paragraph 2).

Wraith et al. reviews the evidence concerning the association between vaccination and autoimmune disease (Lancet 362: 1659-1666, 2003) (see entire document) and notes a number of principles and limitations on diagnosing or reducing vaccine-related autoimmune disease, which has to be assessed on a case-by-case basis (e.g., see How Can a doctor assess a potential link on page 1664) and that a clear distinction should be made between autoimmunity and autoimmune disease (e.g., see Concluding Remarks on page 1665).

Also, see Panel 1: Frequently Asked Questions About Autoimmunity and Autoimmune Diseases on page 1660 as follows.

Autoimmunity is a situation characterized by the development of one or several abnormal immune responses, directed against antigenic components of the host. Autoimmunity can lead to autoantibodies (antibodies against host antigens) or to autoreactive T cells (lymphocytes). Autoimmunity is not always result in autoimmune disease.

Autoimmune disease is a disease that results from autoimmunity, when pathogenic autoantibodies or autoreactive T cells (cell-mediated autoimmune disease) can reach corresponding targets (epitopes) with the appropriate configuration of presentation in host tissues.

In discussing Frequently Asked Questions about Vaccination and Autoimmunity (see Panel 3: Frequently Asked Questions About Vaccination and Autoimunity on page 1661), Wraith notes the following:

In response as to which autoimmune disease, if any, have been proven due to vaccines;
it was noted that an Acute disseminated encephalomyelitis in 0-1% of a form of rabies vaccine, cases of Guillain-Barre neuritis arising after vaccines with swine influenza virus (albeit a rare event), and autoimmune thrombocytopenia has been described

In response to as to how can one demonstrate or exclude that a vaccine caused an autoimmune disease;
it was noted that only epidemiological studies or clinical trials with an extremely large sample size can allow for a consistent assessment of the relative risk of vaccine-related increased incidence, wherein such studies with large sample size are complex, difficult to do and costly, which limit their availability as to how can one demonstrate or exclude that a vaccine caused an autoimmune disease.

In response as to whether minimum criteria be established for diagnosing vaccine-related autoimmune disease, it was noted that there exist no general criteria and this question has to be analyzed on a case-by-case basis.

In addressing the proposed link between childhood vaccinations and the development of type 1 diabetes, Hviid et al. concludes based on their study on childhood vaccination in Denmark (N. Eng. J. Med. 350: 1398-1404, 2004) (see entire document, including Abstract and Discussion).

Also, Hviid et al. describes the basis for the proposed link and the lack of evidence supporting this proposed link, including the examples relied upon in the instant specification, as follows on page 1399, column 1, paragraph 2.

A link between childhood vaccinations and the development of type 1 diabetes has been proposed for several reasons. First, there is a temporal association between the widespread introduction of general childhood immunizations and the increase in the incidence of type 1 diabetes in developed countries. Second, it has been observed that specific vaccines prevent type 1 diabetes in murine models and others induce it. And third, some findings suggest an association between infections and type 1 diabetes. In particular, it has been hypothesized that any vaccination after two months of age increases person's risk of type 1 diabetes and that early vaccination (in the first month of life) protects against type 1 diabetes. Vaccination against Haemophilus influenzae type b has been singled out, with claims of clustering of cases of type 1 diabetes three to four years after vaccination. This hypothesis has recently been expanded to include bacille Calmette–Guérin vaccine; measles, mumps, and rubella (MMR) vaccine; and pertussis vaccine. However, the majority of the evidence does not provide support for these specific hypotheses or for any other association between type 1 diabetes and childhood vaccination, yet there have been few analytic studies.

In discussing biomarkers for diagnosing and monitoring autoimmune diseases activity (Biomarkers 10 Supplement 1: S44-S49, 2005) (see entire document),

Prince concludes that many proteins are increased at tissue sites affected by autoimmune diseases, but only a small number of them show promise as useful markers and much more work is need to characterize changes in response to treatment even that progress has been made in relating the levels of these proteins to disease (see Conclusion on page 548).

Prince also notes that autoantibodies are typically not good biomarkers, mainly because they tend to remain detectable, even after successful treatment (e.g., see page S45, lines 1-2).

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pathogenic processes or pharmacological responses to a therapeutic intervention.

Such markers are useful for diagnosis, prognosis, therapy and drug development and must be based on and follow the understanding of the pathological basis of the disease under study. Measures of the disease process are distinguished between those that have utility in clinical care, where they are called biomarkers and those useful in therapeutic trials, where thy are referred to as surrogate end points. The term surrogate marker is confusing. The requirement for a surrogate end point are multiple and difficult to realize. From the particular view of a diagnostic procedure, a biomarker would need to identify individuals at risk of a given disease and monitor progression towards clinically overt disease. This step would be exceptionally useful in a disease of uncertain evolution / etiology. However, markers must monitor disease progression the clinical manifestation and reflect the extent of intervention afterwards. Other ideal characteristics are that such markers should be applicable in terms of screenings, implying a simple and minimally invasive sample acquisition and processing procedures.

See entire document of Biomarkers Definitions Working Groups., Clin. Pharmacol. Ther. 69: 89-95, 2001.

Given that biomarkers / surrogate markers often do not provide sufficient reproducibility and are difficult to standardize,

that difficulties in relying upon biomarkers / surrogate markers relate to the heterogeneity of diseases and multiple targets such as encompassed by the claimed chronic immune-mediated disorders,

that additional obstacles are raised by high variability in the nature of chronic immune-mediated disorders (e.g. autoimmune diseases) and

that the pathophysiological processes of diseases including chronic immune-mediated disorders, are interconnected and any single marker would be insensitive to completely capture the effect of therapeutic applications;

there is insufficient direction on how to make and use the claimed methods of determining an immunization that the affects the incidence or severity of a chronic immune-mediated in treatment groups relative to control groups, based upon comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.

Note, too, that the evidence provided herein indicates that reliance upon the murine models of diabetes described in the specification does not translate to the association of vaccination and human chronic immune-mediated disorders such as autoimmunity, including diabetes, in humans.

There is an insufficient understanding of the pathogenesis of the diseases and markers that would lead the skilled artisan to make a judgment on the clinical factors, correlation of results with the clinical characteristics of the diseases, such as relapse or progression and response to therapy in a field which is controversial and still debated such as the case here concerning the association of chronic immune-mediated diseases such as autoimmune diseases and vaccination, particularly childhood vaccination.

The evidence would indicate that there is an inability to discriminate between determining whether an immunization protocol can affect the incidence or severity of a chronic immune-mediated in treatment groups relative to control group or whether an immunization protocol can be design to affect the incidence or severity of a chronic immune-mediated disorder, broadly encompassed by the claimed methods.

It does not appear that there is sufficient information to set forth the particular immunization schedules, immunogens, markers and parameters to make and use the claimed methods of determining" and "methods of comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group", which can correlate a method of immunization to a particular chronic immune-mediated disorder resulting in an immunization schedules that affect the incidence of severity of a chronic immune-mediated disorder.

In the absence of objective evidence to the contrary and keeping with the nature of evaluating a number of potential immunological markers for determining an immunization that the affects the incidence or severity of a chronic immune-mediated in treatment groups relative to control groups encompassed by the claimed methods,

the skilled artisan would predict that either there is little or no association between immunization schedules and chronic immune-mediated disorders or that there is an overlap between diseased and non-diseased groups.

While the specification discloses a starting point for screening or testing for immunogens, immunization schedules and comparisons including markers to can determine an immunization schedules that affects the incidence or severity of a chronic immune-mediated disorder, the instant disclosure does not set forth sufficient procedures, elements and parameters that will necessarily lead to determine whether an immunization schedule could affect the incidence or severity of a chronic immune-mediated disorder and it does not identify correlations between vaccines and chronic immune-mediated disorders, including the appropriate immunogens, comparisons and markers to provide a sufficient number of species to support the claimed generic methods.

Consistent with the limitations of the murine models that suggest immunization at birth is associated with a decreased risk of diabetes (type I insulin-dependent diabetes mellitus; IDDM)

in associating vaccination with immune-mediated disorders in humans and

consistent with insufficiency of the immunization schedules addressing vaccines to immune-mediated disorders such as diabetes in humans at the time the invention was made,

inventor's co-authored publication (Classen et al., Medical Hypotheses 57: 532-538, 2001) (see entire document, particularly the Conclusion on page 536) concludes with the following.

There are many mechanisms by which vaccines may affect the onset of IDDM or other immune-induced disorders. The predominant pathways may depend on individual genotype. We believe that lack of full comprehension of the mechanism of action does not detract from toxicology data linking vaccines to IDDM, nor does a complete knowledge of the mechanism of action need to be known before studying the potential benefits of new immunization schedules.

Here, Classen et al. recognize that immune-induced disorders may depend on individual genotypes and that immunization schedules addressing the association between immunization and immune-mediated disorders was still at the potential stage subsequent to the time the invention was made.

While the specification discloses a starting point for screening or testing for immunogens, immunization schedules and comparisons including markers to can determine an immunization schedules that affects the incidence or severity of a chronic immune-mediated disorder,

the instant disclosure does not set forth sufficient procedures, elements and parameters that will necessarily lead to determine whether an immunization schedule could affect the incidence or severity of a chronic immune-mediated disorder and it does not identify correlations between vaccines and chronic immune-mediated disorders, including the appropriate immunogens, comparisons and markers to provide a sufficient number of species to support the claimed generic "methods of comparing".

The application does no more than describe the desired function or endpoints of the claimed "methods of comparing the incidence..." and/or "methods of comparing the risk..." broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors have enabled the claimed kits relying upon these "methods of comparing" commensurate in scope with the claimed invention.

The claimed "methods of comparing the incidence..." and/or "methods of comparing the risk..." depend upon finding "an immunization schedule could affect the incidence or severity of a chronic immune-mediated disorder and it does not identify correlations between immunogens/vaccines and chronic immune-mediated disorders", including the reliance upon the appropriate immunogens (including those specifically recited), comparisons and markers.

Without the appropriate immunogens, comparisons and markers, the skilled artisan cannot practice the claimed kits relying upon "methods of comparing the incidence..." and/or "methods of comparing the risk...". It means little to invent a method if one does not have possession of the elements, parameters and comparisons that are essential to practice the method.

Without sufficient guidance and direction as to how to make and use the claimed comparisons and/or correlations between vaccination / immunization and chronic immune-mediated disorders,
it would have been unpredictable to the skilled artisan at the time the invention was made to correlate a method of immunization to a particular chronic immune-mediated disorder resulting in an immunization schedules that affect the incidence of severity of a chronic immune-mediated disorder.

The specification describes assays for determining whether a method of immunization schedules that affect the incidence of severity of a chronic immune-mediated disorder and identifies some broad categories of certain correlations between vaccines and chronic immune-mediated disorders as well as a murine mode that might work (though the murine model has not been supported in humans as addressed herein),
this description of screening assays without more precise guidelines amount to little more that a starting point, a direction for further research.

The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention.

The scope of the required enablement varies inversely with the degree of predictability involved and in cases involving unpredictable factors such as physiological activity more may be required. See MPEP 2164.03 and 2164.02.

Given the relatively incomplete understanding in the biotechnological field involved and the lack of a reasonable correlation between the narrow disclosure in the specification and broad scope of protection sought in the claims; the lack of enablement is deemed appropriate.
See MPEP 2164.08.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In view of the lack of predictability of the art to which the invention pertains, methods of determining" with respect to a broad variety of diverse immunogens, markers, comparisons and disorders would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective methods to correlate a method of immunization to a particular chronic immune-mediated disorder resulting in an immunization schedules that affect the incidence of severity of a chronic immune-mediated disorder, undue experimentation would be required to practice the claimed "methods of comparing the incidence..." and/or "methods of comparing the risk..." recited in the context of the claimed kits with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed "methods of comparing the incidence..." and/or "methods of comparing the risk..." and absent working examples providing evidence which is reasonably predictive that the claimed "methods of comparing" are effective for correlating a method of immunization to a particular chronic immune-mediated disorder resulting in an immunization schedules that affect the incidence of severity of a chronic immune-mediated disorder, broadly encompassed by "the claimed methods of comparing".

B) Protect against events at least two infectious diseases an infectious disease" and prophylactically: Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of an immunogen or immunization schedule can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo experimental observations as well as the clinical experience accurately reflects the relative ability or efficacy of the claimed methods to prevent at an infectious disease / at least two infectious diseases, as it reads on protect against an infectious disease(s).

"Prophylactically" recited in independent claims 318 is viewed the same or nearly the same as "protect".

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively to prevent at an infectious disease / at least two infectious diseases, as it reads on protecting against an infectious disease(s), particularly with any immunogen or immunization schedule, particularly in humans. The specification does not teach how to extrapolate data obtained from various in vitro or in vivo observations with certain immunogens and certain infectious diseases to the development of effective methods to prevent at an infectious disease / at least two infectious diseases, as it reads on preventing an infectious disease(s).

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the infection and the modulation of the host immune system occur at the same or nearly the same time. Protecting against certain infectious diseases are much easier to achieve under such controlled conditions that experienced in the population as a whole as well as with any immunogen / immunization schedule encompassed by the claimed invention

There is insufficient guidance and direction as well as objective evidence to provide for to preventing an infectious disease / at least two infectious diseases, as it reads on protecting an infectious disease(s) with any immunogen / immunization schedules and given the diversity and scope of infectious diseases encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to prevent at an infectious disease / at least two infectious diseases, as it reads on protecting against an infectious disease(s) with any immunogen / immunization schedule, undue experimentation would be required to practice the claimed methods of protecting against infectious disease(s) with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for prevent the infectious diseases encompassed by the claimed methods and products.

Applicant is invited to amend the claims to avoid the recitation of "protect" and "prophylactically.

12. Petition Under 37 CFR 1.181 For Supervisory Review.

Applicant's Petition Under 37 CFR 1.181 For Supervisory Review, filed 07/01/2009, is acknowledged.

With respect to applicant's arguments, in conjunction with the Classen Declaration under 37 CFR 1.32, filed 10/08/2002 as it reads on the current rejections under 37 CFR 112, first paragraph, written description and enablement, the following is noted.

While applicant relies upon experimental, veterinary and epidemiological evidence to support the association between vaccination/immunization and chronic immune-mediated immune disorders such as autoimmune diseases,

the evidence presented herein above clearly addresses the limitations of such association as it reads human vaccination and autoimmune diseases and clearly addresses the specific teachings of Classen.

While applicant relies upon applicant's own statistical analyses and re-analyses of various studies, the evidence above has also relied upon statistical analyses to counter applicant's assertions of an association between immunization / vaccination and chronic immune-mediated disorders / autoimmunity in humans.

Comparison of statistical analyses as determined by applicant and the evidence from several sources above is difficult since the Office is not equipped to conduct those comparisons.

Consistent with the limitations of the murine models that suggest immunization at birth is associated with a decreased risk of diabetes (type I insulin-dependent diabetes mellitus; IDDM)

in associating vaccination with immune-mediated disorders in humans and

consistent with insufficiency of the immunization schedules addressing vaccines to immune-mediated disorders such as diabetes in humans at the time the invention was made,

inventor's co-authored publication (Classen et al., Medical Hypotheses 57: 532-538, 2001) (see entire document, particularly the Conclusion on page 536) concludes with the following.

> There are many mechanisms by which vaccines may affect the onset of IDDM or other immune-induced disorders. The predominant pathways may depend on individual genotype. We believe that lack of full comprehension of the mechanism of action does not detract from toxicology data linking vaccines to IDDM, nor does a complete knowledge of the mechanism of action need to be known before studying the potential benefits of new immunization schedules.

While applicant has relied upon this same paper to support the claimed invention;

here, Classen et al. recognize that immune-induced disorders may depend on individual genotypes and that immunization schedules addressing the association between immunization and immune-mediated disorders was still at the potential stage subsequent to the time the invention was made.

While the specification discloses a starting point for screening or testing for immunogens, immunization schedules and comparisons including markers to can determine an immunization schedules that affects the risk, incidence, frequency or severity of a chronic immune-mediated disorder,

the instant disclosure does not set forth sufficient procedures, elements and parameters that will necessarily lead to determine whether an immunization schedule could affect the incidence or severity of a chronic immune-mediated disorder and it does not identify correlations between vaccines and chronic immune-mediated disorders, including the appropriate immunogens, comparisons and markers to provide a sufficient number of species to support the claimed generic "methods of comparing" under 35 U.S.C. 112, first paragraph, written description and enablement for the reasons explained in more detail above.

Applicant's arguments have not been found persuasive.

13. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Eckhart et al. (EP 0484621) in view of Madore et al. (Pedriatics 85: 331-337, 1990) (of record), Kniskern et al. (U.S. Patent No. 5,847,112), Lyson (U.S. Patent No. 4,748,019), Do Couto et al. (U.S. Patent No. 5,804,187) and Otto (U.S. Patent No. 5,616,578).

Eckhardt et al. teach vaccine, including Bordetella pertussis which combines pertussis antigens filamentous hemagglutinin, detoxified lymphocytosis promoting factor and a 69 kilodalton outer membrane protein (see entire document, including Summary of the Invention and Detailed Description of the Invention). In addition Eckhardt et al. teach including other vaccine components including diphtheria toxoid, Haemophilus antigens, Neisseria meninococcus , Pneumococcus and Hepatitis B (e.g., see column 4, paragraph 4,) as well as vaccines comprising adjuvants, including aluminum (e.g., see column 4, paragraph 5). Note, too, that the vaccines comprises various structural components including saccharides (e.g., see column 4, paragraph 2) (see entire document)

Eckhardt et al. differs from the claimed invention by not describing kits and conjugate vaccines per se.

With respect to the known use of conjugates,

Kniskern et al. teach the well known use of conjugates and carrier proteins associated with vaccines, including its use with Streptococcus pneumoniae, including the use aluminum in conjugate vaccines (e.g., see column 13, paragraph 5) and its applicability to other pathogens such as Neisseria meningitides B, streptococci and other opportunistic infections (e.g., see column 14, paragraph 1) (see entire document, including Background of the Invention, Summary of the Invention and Detailed Description of the Invention).

In addition, Madore et al. teach Haemophilus influenza type b oligosaccharide conjugates as a meningitis vaccine (see entire document, including Vaccine on pages 331-332 and Tables 1-5)

With respect to kits,

Lyson teaches the known use of placing vaccines into kits (e.g., see column 2, paragraph 3 and Claims).

In addition, Do Cuoto et al. teach the use of vaccination kits (e.g., see Abstract and column 43, paragraph 2).

In addition, it was well known in the art to provide components such as containers and labels with kits, as taught by Otto (e.g., see column 41, paragraph 3)

With respect to the process and intended use elements of the claimed kits and methods of making kits, the following is noted.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

The printed matter on a label or package insert does not lend patentable weight as a limitation of the claimed product, composition, or article of manufacture, absent a functional relationship between the label or package insert and the product, composition, or article of manufacture.

Applicant's arguments, filed 09/21/2009, including the weight of the functional relationship of the printed matter as they would apply to the New Grounds of Rejections set forth herein has not distinguished the structural elements of the claimed invention from the prior art.

The instructions carry little weight absent evidence of structural differences.

While applicant asserts that without the claimed directions for use, the clinician would not know how to use it limit the increase incidence or severity of the disorder attributable to late immunization,

the claims are drawn to kits comprising immunogens or vaccines, wherein the structure of the immunogens or vaccines are not changed and/or wherein the structure of the immunogens or vaccines meet the asserted intended use or product-by-process limitations, absent evidence to the contrary.

For example, applicant's own disclosure and/or papers based upon epidemiologic studies would indicate that standard vaccinations do not necessarily result in chronic immune-mediated disorders or autoimmunity.

Also, given the absence of any particular disorder recited, there is a broad breadth of disorders encompassed by the intended use or product-by-process limitations.

Furthermore, with respect to the step of "comparing the risk, incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group", the following is noted.

These instant claims are drawn to kits or methods of making kits.

It is noted that this "comparing" step or clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or may be performed entirely in the human mind is obviously not tied to any machine and does not transform any article into a different state or thing.

Therefore, the "comparing" steps or clauses are not found to further limit the claimed kits of methods of making a kit as defined by the claims, since it simply expresses the intended result of a process step positively recited (e.g., "immunizing" or "vaccinating").

Consistent with the disclosure of the instant application, the "comparing" steps can be determined by mere inspection and do not require performing experimental or clinical tests that are transformative.

The mental steps of "comparing" do not negate the kits or making the kits comprising immunogens, but has been given it has been given proper patentable weight in light of the statements noted herein.

Given the teachings of the prior art, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the well known use of the same or nearly the same conjugation as encompassed by the claims to a number of vaccines, including those specific immunogens recited in the instant claims

Given the teachings of the prior art, one of ordinary skill in the art would have provided kits to a number of different immunogens / vaccines as a means of convenience and economy, including the provision of containers, labels or written materials such as instructions.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements such as known immunogens/vaccines, vaccine conjugates and kits were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods of conjugating vaccines of interest and placing them in kits for convenience and economy with no change in their respective functions and the combination would have yielded nothing more than predictable results of achieving the goals of providing vaccines of interest to ameliorate the effects of infection by various pathogens, while diminishing the adverse effects of such vaccines

The rationale to support a conclusion that the claims would have been obvious is that immunogens / vaccines, vaccine conjugates and kits were made part of ordinary capabilities of one skilled in the art based upon the teachings of the prior art. One of ordinary skill in the art would have been capable of applying the known approaches to conjugate vaccines of interest or to provide vaccines in kits, which would have been predictable to one of ordinary skill in the art at the time the invention was made.

The rationale to support a conclusion that the claims would have been obvious is that a particular known techniques of conjugating vaccines to determine the most beneficial and least detrimental immunization / vaccination protocols to ameliorate the effective of infection by various pathogens was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying these known techniques to known vaccines that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options of conjugating vaccines or placing them in kits within his or her technical grasp. This leads to the anticipated success of providing for vaccine conjugates and vaccine kits. It is likely the product not of innovation but of ordinary skill and common sense.

Since testing and comparing vaccines would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of vaccines conjugates that would be the most beneficial and least detrimental immunization / vaccination protocols to ameliorate the effective of infection by various pathogens. The prior art had recognized the advantages of vaccine conjugates to accomplish this goal. The claims were obvious because it would have been obvious to try testing and comparing vaccine formulations to determine the most beneficial and least detrimental vaccines to ameliorate the effective of infection by various pathogens with a reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable
over claims 1-4, 7-22, 24-26, 28-29, 32-36, 39-43, 46-50, 53-189, 196 and 228-273 of USSN 10/662,072;
over claims 139 and 1445 of USSN 11/547,720;
over claims 1-63 of USSN 12/421,073;
over claims 1-6, 9-13, 16, 19-32, 34-92, 98-103, 107-109 and 112-123 of USSN 12/435,122 and
over claims 1-35 of USSN 12/444,232.

The pending claims of the instant and copending applications are drawn to the same or nearly the same products and/or methods of using products that are involved with the same or nearly the same immunizations against infectious diseases and can reduce the incidence, severity of the same or nearly the same chronic immune-mediated disorders.

With respect to any differences in immunization schedules or screening procedures between copending claims, the following is noted.

Immunizing subject against infectious diseases as elements of immunization / vaccination to induce responses to known infectious diseases while decreasing adverse effects of such immunization / vaccination procedures were result effective variables.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989).

As immunization to induce desired immune responses and avoid / diminish adverse responses were known and practiced by the ordinary artisan at the time the invention was made, it would have been obvious to optimize both the nature of the immunogens and the mode of administration as well as dosage amounts of said immunogens in vaccination schedules to induce the appropriate immune responses to known infectious diseases and to diminish adverse effects associated with such vaccinations procedures.

Given the recitation of the same or nearly the same products in the copending method claims, the copending method claims anticipate or render obvious the instant product claims.

While the instant claims recite a kit, no positive recitation of the ingredients distinguishes it over the other claims that encompass methods or compositions comprising the same or nearly the same immunogens. Also, it has been a well known convention in the art to place these components in a pack for convenience and economy.

Also, it is noted the continuations and continuations-in-part have been filed in related Classen applications.

A number of terminal disclaimers have been filed in the Classen applications and U.S. Patents.

Applicant is reminded that the protection afforded by Section 121 to applications (or patents issued therefrom) filed as a result of a restriction requirement is limited to divisional applications. Pfizer Inc. v. Teva Pharmaceuticals Inc., 518 F.3d 1353, 1362, 86 USPQ2d 1001, 1007-1008 (Fed. Cir. 2008).

Applicant is reminded that the prohibition against double patenting rejections under 35 U.S.C. 121 does not apply even) when the requirement for restriction (holding of lack of unity of invention) was only made in an international application by the International Searching Authority or the International Preliminary Examining Authority.

However, there does not appear to have been a hold of lack of unity of invention either at the PCT or 371 level of prosecution.

Further, it is noted that applicant prosecuted both methods and products for eight (8) years.

Applicant's remarks, filed 09/21/2009, concerning double patenting is not found persuasive given the long prosecution of both products and methods in the instant application as well as the reasons set forth herein.

17. Claims 59-61, 84, 108, 116, 277-279, 281, 292, 294, 298, 299-301 and 304-324 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 1-42 of U.S. Patent No. 5,728,385 (892; of record),
over claims 1-70 of U.S. Patent No. 6,420,139 (892; of record),
over claims 1-108 of U.S. Patent No. 6,638,739 (892; of record) and
over claims 1-213 of U.S. Patent No. 7,008,790 (892; of record).

The pending claims of the instant and copending applications are drawn to the same or nearly the same products and/or methods of using products that are involved with the same or nearly the same immunizations against infectious diseases and can reduce the incidence, severity of the same or nearly the same chronic immune-mediated disorders.

With respect to any differences in immunization schedules or screening procedures between copending claims, the following is noted.

Immunizing subject against infectious diseases as elements of immunization / vaccination to induce responses to known infectious diseases while decreasing adverse effects of such immunization / vaccination procedures were result effective variables.

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215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989).

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However, there does not appear to have been a hold of lack of unity of invention either at the PCT or 371 level of prosecution.

Further, it is noted that applicant prosecuted both methods and products for eight (8) years.

Applicant's remarks, filed 09/21/2009, concerning double patenting is not found persuasive given the long prosecution of both products and methods in the instant application as well as the reasons set forth herein.

18. No claim allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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